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*THE DEPENDENCE OF PROTECTION AGAINST A TRANSPLANTABLE MOUSE LEUKEMIA UPON THE GENETIC CONSTITUTION OF THE IMMUNIZING TISSUE**

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Populations of leukemic cells, as other malignant growths, can be maintained indefinitely by successive transfers from host to host of a susceptible strain, and these hosts can be rendered resistant by prophylactic treatment with sublethal doses of leukemic cells[1] as well as with normal tissue.[2] The extensive studies of L. Loeb and associates on normal tissue transplantation indicate that the nature of the host response varies with the constitution of the graft. Their studies, based on direct microscopic observations, might lead one to expect a similar dependence upon the constitution of the graft when the host response is tested physiologically by a subsequent inoculation with malignant cells. However, in no such case has the induced resistance to malignant growth been shown to depend significantly upon the constitution of the immunizing tissue. Schöne[3] stated that normal tissue from the same strain as the host gave a stronger immunity to a transplantable mouse carcinoma than tissue from another strain. Donaghy and Hyde[4] found immunity to Walker's rat sarcoma induced by tissue of the host strain was possibly less strong (17:3) than that induced by tissue of another strain (20:0). But in these cases, although the strains may have been "inbred," the possibility remains that the individuals from the same strain were not genetically alike. With impure biological materials, as with impure chemicals, significant relationships may be hidden.

By the use of mouse strains whose genetic homogeneity is indicated by the many years of exclusively brother by sister matings and demonstrated by numerous experimental tests, it is found that every mouse in a strain that is 100% susceptible can be protected against a given line of transplantable leukemia by treatment with tissue of a certain genetic constitution, while under the same conditions tissue of another genetic constitution does not protect a single mouse.

This report is limited to resistance induced by normal embryo tissue against leukemia of line I in hosts of strain C58. These hosts are 100% susceptible to standard dose of leukemic cells of line I in over 3000 tested in the last four years, as well as to $^1/_{64}$th of the standard dose (97 tested). The treatment with embryo tissue consisted of a single intraperitoneal injection of a saline suspension of minced skin and/or viscera of embryos shortly before term; 0.5 cc. saline was used for skin or viscera of each embryo; 0.5 cc. of the suspension was given to each mouse. The test inoculation of leukemic cells was administered 6–9 days after the embryo tissue, in doses $^1/_{64}$th of the standard. The untreated controls and the unsuccessfully treated test animals died $5^1/_2$ to $6^1/_2$ days after leukemic inoculation; the remainder were observed for at least thirty days.

TABLE 1

IMMUNIZATION BY EMBRYO TISSUE AGAINST INOCULATED LEUKEMIA

Dose = $^1/_{64}$th standard of leukemic cells of line I. Hosts = strain C58

STRAIN OF EMBRYOS	NO. OF EXPTS.	NUMBER OF MICE SURVIVED	NUMBER OF MICE DIED
—	24	0	104
StoLi	10	93	0
C58	9	0	75
F_1(C58 × StoLi)	7	80	0

Table 1 indicates that the embryos from strain StoLi have successfully induced resistance in all cases; that embryos from the same strain as the hosts (C58) have completely failed to induce resistance; that hybrid embryos (C58 mother by StoLi father) are as successful as those from strain StoLi. The uniformity of these results bespeaks the successful control of technique and of the biological variables of the embryos, the hosts and the leukemic cells. The major basis for judging significance lies in the number of experiments, each of which is an independent repetition; these cover a period of eight months.

Natural susceptibility as hosts and failure to induce resistance as embryos are associated in strain C58, but the connection is not causal, for the hybrid embryos induce resistance and yet are naturally susceptible (100%) when used as hosts.

* Aided by a grant from the Carnegie Corporation.

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[2] Rhoads, C. P., and Miller, D. K., *Ibid.*, **32**, 817 (1935).

[3] Schöne, G., *Verhandl. Gesel. deut. Naturforsch. Aerzte*, **79**, 304 (1907).

[4] Donaghy, F., and Hyde, R. R., *Am. Jour. Hyg.*, **14**, 495–501 (1931).

ON THE CHAINS OF A COMPLEX AND THEIR DUALS

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Let C be a finite or infinite topological complex. With each i-cell of C we shall introduce a pair of symbols $E^{(i)}_s$ and $F^s_{(i)}$. An *i-chain* will be any finite linear combination of symbols of the first kind,

$$K^{(i)} = \sum_s \alpha^s E^{(i)}_s, \tag{1}$$

where the coefficients α^s are elements of any preassigned additive group A. An *i-function* will be any linear combination, finite or infinite, of symbols of the second kind,

$$L_{(i)} = \sum_s \beta_s F^s_{(i)}, \tag{2}$$

where the coefficients β_s are elements of the character group B of A (the group of all representations of A on the unit circle in the complex plane). If we designate the points of the unit circle by a real parameter λ, modulo 1, we can construct a bilinear form

$$(\beta_s, \alpha^t) = \lambda^t_s, \quad (\text{mod } 1), \tag{3}$$

such that λ^t_s is the point on which the character β_s maps the group element α^t. We can then form the expression

$$(L_{(i)}, K^{(i)}) = \sum_s (\beta_s, \alpha^s), \quad (\text{mod } 1), \tag{4}$$

which will be called the *integral* of $L_{(i)}$ over $K^{(i)}$.

The classical theory of connectivity may be summarized as follows. We orient the cells of C and denote by

$$\{E^{(i)}_s, F^t_{(i-1)}\}, \quad (= 0, 1, -1), \tag{5}$$

the incidence number between the oriented i-cell associated with $E^{(i)}_s$ and the oriented $(i-1)$-cell associated with $F^t_{(i-1)}$. We then define a linear operator β transforming an i-chain $K^{(i)}$ into an $(i-1)$-chain

$$\beta K^{(i)} = \sum_{s,t} \alpha^s \{E^{(i)}_s, F^t_{(i-1)}\} E^{(i-1)}_t, \quad \begin{pmatrix} \alpha^s.1 = \alpha^s \\ \alpha^s.0 = 0 \end{pmatrix}, \tag{6}$$

called the *boundary* of $K^{(i)}$. The chain $K^{(i)}$ is said to be *closed* if its boundary vanishes; it is said to be *bounding* if there exists any $K^{(i+1)}$ such that $\beta K^{(i+1)} = K^{(i)}$. The incidence numbers (5) satisfy the well-known relations

$$\sum_t \{E_s^{(i)},\ F_{(i-1)}^t\}\ \{E_t^{(i-1)},\ F_{(i-2)}^u\} = 0, \tag{7}$$

from which we obtain, at once,

$$\beta^2 K^{(i)} = 0. \tag{8}$$

By (8), the group Ψ^i of all bounding i-cycles is a subgroup of the group Φ^i of all closed i-cycles. The group $\Phi^i \bmod \Psi^i$ is the *i-th connectivity group* of C.

We now propose to introduce a new linear operator δ dual to β. The operator δ will transform an i-function $L_{(i)}$ into an $(i+1)$-function

$$\delta L_{(i)} = \sum_{s,t} \beta_s \{E_t^{(i+1)},\ F_{(i)}^s\}\ F_{(i+1)}^t, \tag{9}$$

which will be called the *derived* of $L_{(i)}$. We shall say that $L_{(i)}$ is *exact* if its derived vanishes and that it is *derived* if there exists any $L_{(i-1)}$ such that $\delta L_{(i-1)} = L_{(i)}$. By (7), the operator δ satisfies the relation

$$\delta^2 L_{(i)} = 0, \tag{10}$$

dual to (8). Thus, we see that the group Ψ_i of all derived i-functions is a subgroup of the group Φ_i of all exact i-functions. We call the group $\Phi_i \bmod \Psi_i$ the *dual* of the i-th connectivity group of C. *This group is easily seen to be the character group of the i-th connectivity group.*

Let $K^{(i)}$, cf. (1), be an arbitrary i-chain and $L_{(i-1)}$ an arbitrary $(i-1)$-function,

$$L_{(i-1)} = \sum_s \gamma_s F_{(i-1)}^s. \tag{11}$$

Then, by a simple computation, we obtain the relation

$$(\delta L_{(i-1)},\ K^{(i)}) = (L_{(i-1)},\ \beta K^{(i)}) = \sum_{s,t} \{E_t^{(i)},\ F_{(i-1)}^s\}\ (\gamma_s \cdot \alpha^t), \tag{12}$$

which says that *the integral of the derived of $L_{(i-1)}$ over $K^{(i)}$ is equal to the integral of $L_{(i-1)}$ itself over the boundary of $K^{(i)}$*. By (8), (10) and (12), we also have the corollary: *the integral of a derived function $\delta L_{(i-1)}$ over a closed chain $K^{(i)}$ is always zero; likewise, the integral of an exact function $L_{(i-1)}$ over a bounding chain $\beta K^{(i)}$*. The integral of an exact $L_{(i)}$ over a closed $K^{(i)}$ will be called the *period* of $L_{(i)}$ over $K^{(i)}$. It will, in general, be different from zero.

Formula (12) is analogous to the well-known theorem of Stokes on multiple integrals. The coefficients α^s and γ_s in (1) and (11) need not be chosen in exactly the manner indicated above. If we take the coefficients α^s to be arbitrary integers and the coefficients γ_s to be arbitrary real numbers, and if we write, in place of (3), the relation

$$(\gamma_s, \alpha^t) = \gamma_s \alpha^t, \text{ (not reduced mod 1)}, \tag{13}$$

then (12) becomes the exact analogue of the theorem on multiple integrals and reduces to the latter by a passage to the limit.

ON THE RING OF A COMPACT METRIC SPACE

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Let C be a compact metric space. We pick an arbitrary additive group A and define an *i-function* of C to be any single-valued, skew symmetric function,

$$F(p_0p_1 \ldots p_i), \tag{1}$$

of $i + 1$ variable points of C, where the values of F are elements of A. (For the case $i = 0$ the function F is an ordinary point function on C.) The function F will be said to be *locally zero*,

$$F = 0 \text{ (locally)}, \tag{2}$$

if there exists an $\epsilon > 0$ such that F vanishes whenever the distances between the points p_s ($s = 0, 1, \ldots, i$) are all less than ϵ. Given any i-function F we construct an $(i + 1)$-function δF which we call the *derived* of F and which we define by the formula

$$\delta F(p_0p_1 \ldots p_{i+1}) = \frac{1}{(i+1)^i} \sum_s (-1)^s F(p_0p_1 \ldots p_{s-1}p_{s+1} \ldots p_{i+1}). \tag{3}$$

We say that F is *exact* if δF is locally zero. For the case $i > 0$, we say that F is *derived* if there exists any $(i-1)$-function G such that $\delta G = F$. For the case $i = 0$, we say that F is *derived* if it is constant over C. By the skew symmetry of F we have, at once,

$$\delta^2 F = 0, \tag{4}$$

from which we conclude that *every derived function is exact.* Now, the exact i-functions on C form a group Φ_i with respect to addition and, by (4), the derived i-functions form a subgroup Ψ_i of Φ_i. We form the group $\Phi_i \bmod \Psi_i$. *This group is a topological invariant analogous to the i-th connectivity group of C,* as defined by Vietoris. In fact, if the coefficients of the Vietoris cycles are taken to be elements of the character group B of A, then *the i-th connectivity group of C may be identified with the character group of the group* $\Phi_i \bmod \Psi_i$.

A more interesting invariant can be obtained when A is the group of a ring, so that the elements of A can be both added and multiplied. We

may then define the *cross-product* $F \times G$ of an i-function F and a j-function G by the formula

$$F \times G = \frac{1}{(i+1)!(j+1)!} \Sigma(-1)^{N_\alpha} F(p_0 \ldots p_i) G(q_0 \ldots q_j), \quad (5)$$

where the sum is extended over all permutations of the $i + j + 1$ points p_s and q_t and where the index N_α is 0 or 1 according as the permutation is even or odd. The products FG in the right-hand member of (5) are, of course, the ordinary products of elements in the ring of A. From (5), we have, at once,

$$F \times (G \times H) = (F \times G) \times H \quad (6)$$

and

$$F \times G = \pm(G \times F), \quad (7)$$

where the sign of the right-hand member of (7) is a function of the dimensionalities of F and G. With (5) as our definition of multiplication, the combined i-functions of C of all dimensionalities form a ring R.

The operator δ defined by (3) may be given the following simple interpretation. We write

$$\delta F = \delta \times F, \quad (8)$$

and treat the symbol δ in the right-hand member of (8) as a point function with the value 1 everywhere on C. (The function will be symbolic if 1 is not in the ring of A but, in all cases, it will have a meaning when combined with a function F. If a is a value of F then, of course, we write $\pm 1a = \pm a$.) Now, by (6) and (7), we have

$$\delta(F \times G) = \delta F \times G = \pm(F \times \delta G) \quad (9)$$

from which we conclude that

$$\delta G = 0 \text{ implies } \delta(F \times G) = 0. \quad (10)$$

Relation (10) tells us that the exact i-functions of all dimensionalities form an ideal J_Φ within the ring R. Moreover, by (9), the derived i-functions form an ideal J_Ψ within the ring formed by the ideal J_Φ. Therefore, finally, there exists a ring $J_\Phi \bmod J_\Psi$. We shall call this last ring *the ring of the point set* C. It fully determines the groups $\Phi_i \bmod \Psi_i$ and their character groups, the connectivity groups. It is, however, a stronger invariant than the latter.

ON THE REPRESENTATION OF POSITIVE HARMONIC FUNCTIONS

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The problem of representation of the positive harmonic function in a given bounded region (non-vacuous, open, connected set) is interesting not only *per se* but also because of its relevance to other important problems of potential theory.

Any positive harmonic function $U(P)$ in a region A which region satisfies the conditions given below is of the form

$$U(P) = \int_{A^*} f(S, P)\, d\,\mu(e_s),^1 \qquad (1)$$

where A^* is the boundary of A and $f(S,P)$ is a function depending only on A and defined for $S \epsilon A^*$, $P \epsilon A$; $\mu(e)$ is a non-negative completely additive function of Borel sets which is zero in the complement, $-A^*$, of A^*. It is to be emphasized that this result is independent of the number of dimensions.

We denote by $E(U(P), A)$ the set of points S of A^* for which $\lim_{P \to S, P \epsilon A} U(P) > 0$, where $U(P)$ is non-negative and harmonic in A. $U(P)$, $V(P)$, etc., denote non-negative harmonic functions throughout.

For (1) the following conditions are sufficient:

(α) The classical Dirichlet problem is solvable for A.

(β) Every boundary point, S_0, of A admits the so-called "principle of Picard," i.e., if $S_0 \epsilon A^*$ and $E(U(P), A) = E(V(P), A) = \{S_0\}$, then $U(P) = C \cdot V(P)$, where C is a positive constant.

(γ) If $U_n(P) \longrightarrow U(P)$ in A, and if B is a closed set such that for each n $E(U_n(P), A) \subset B$, then $E(U(P), A) \subset B$.

(δ) There exists for A a sequence of approximating regions $A_1, A_2, \ldots$, having the following properties:

(i) $A_n \subset \overline{A}_{n+1} \cdot A$, (ii) $\lim_{n \to \infty} A_n = A$, (iii) each A_n satisfies (α), (β) and (γ), (iv) if $U_n(P)$ is defined in A_n and if B is a closed set such that for each n $E(U_n(P), A_n) \subset B$, then for any subsequence $\{U'_n(P)\}$ of $\{U_n(P)\}$ for which $U'_n(P) \to U(P)$ in A we shall have $E(U(P), A) \subset B$.

If (α), (β), (γ) and (δ) hold, $f(S,P)$ can be chosen continuous and equivalent in A^* to a derivative $dm(e_s; P)/dm(e_s; P_0)$ where $m(e; P)$ is the mass distribution on A^* obtained by sweeping out a unit mass at P on to A^*; P_0 is a fixed point in A. With this choice of $f(S, P)$, to each $U(P)$ in A there is one and only one $\mu(e)$ with $\mu(e(-A^*)) = 0$, that is, the correspondence by (1) between $U(P)$ and $\mu(e)$ is one–one.

If the representation (1) has the property that $f(S, P)$ is equivalent to the derivative $dm(e_s; P)/dm(e_s; P_0)$ and if it is to have the further property that for closed subsets B of A^*, $\mu(e(-B)) = 0$ implies that the $U(P)$ corresponding to $\mu(e)$ satisfies $E(U(P), A) \subset B$, then (α), (β) and (γ) are necessary for (1).

It can be shown by direct analysis that if A is a bounded plane region bounded by a finite number of distinct simple closed Jordan curves, then (α), (β), (γ) and (δ) hold.

A detailed exposition of these results and other applications will appear elsewhere.

[1] Radon, "Theorie und Anwendungen der absolut additiven Mengenfunktionen," *Wiener Sitzber.*, **122**, IIa[2], 1295 ff. (1913).

HUNGER-CONTRACTIONS AND RATE OF CONDITIONING

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Wide-spread facilitation of reflexes and increase in the efficiency of learning may both result from the incidence of muscular tensions.[1] Many of the effects of muscular tension are also produced by those periodic changes in gastric tonus which are known as "hunger-contractions."[2] The hypothesis has been put forward[3] that one and the same mechanism is involved in the effects of muscular tensions and of hunger-contractions. In both cases there are muscular tensions which give rise to volleys of afferent nervous impulses that result in central and peripheral facilitation. All the available evidence indicates that the facilitatory effects of these two conditions are identical. However, there has been no experiment that demonstrates the effect of hunger-contractions upon learning, and the present study was undertaken to remedy this lack.

Male albino rats of the Wistar strain were given double stimulations of electric shock and light. The unconditioned stimulus, an electric shock, evoked the response of jumping from one part of the cage to another. The conditioned stimulus, an electric light, at first elicited no detectable response. Each rat was placed in an activity cage and deprived of food for 24 hours prior to experimentation. An automatic timing device delivered the stimuli mechanically and at irregular time intervals. The shock and the light were presented simultaneously, about 50 times in an hour. After every fourth or fifth stimulation the light was presented alone as a test. Separate writing levers recorded the two stimulations

and the response on a kymograph. The conditioning series was continued until one clear-cut conditioned response appeared when the light was presented alone.

In order to be certain of the appearance of hunger-contractions the stomachs of fourteen rats were transplanted to a position just below the skin, following the procedure used by Powelson.[4] With this hernia it was possible to observe the hunger-contractions directly. Nine rats that recovered from the operation were placed in activity cages and deprived of food for 24 hours. The activity was recorded and observations were made on the hunger-contractions. Each rat showed from 10 to 18 periods of activity in 24 hours at fairly regular intervals. The periods of activity varied in length from 15 to 30 min. In further confirmation of the findings of Richter[5] and Powelson[6] the activity was found to coincide with periods of

TABLE 1

FACILITATION OF LEARNING BY CONCOMITANT HUNGER-CONTRACTIONS

RATS WITHOUT CONTRACTIONS	NO. OF TRIALS FOR CONDITIONING	RATS WITH CONTRACTIONS	NO. OF TRIALS FOR CONDITIONING
No. 3	53	No. 10	24
No. 6	56	No. 9	21
No. 2	51	No. 7	34
No. 4	75	No. 18	18
No. 12	57	No. 11	25
No. 13	30	No. 53	30
No. 14	71	No. 41	18
No. 5	*50+		
	Mean: 55.4		Mean: 24.3

* Rat No. 5 gave no indication of conditioning after 50 trials and the series was then discontinued. The behavior of this rat was exceptional in that by the 50th trial all response to the shock had stopped and there appeared to be little hope of establishing a conditioned response.

hunger-contractions. The correspondence was so definite that additional unoperated rats were utilized in the conditioning experiment and the onset of the periodic activity was accepted as an index of hunger-contractions.

In the conditioning experiment the rhythms of activity were recorded during the 24-hour fast. At the beginning of an outburst of activity near the end of the 24-hour period the stimulating device was started and the series of stimuli run off until a definite conditioned response was recorded. A control group, without hunger-contractions but in otherwise substantially the same nutritive condition, was created by feeding a small amount of food (0.15 grm.) to alternate animals just before the conditioning routine. As Carlson[7] has shown the introduction of even a small amount of food into the stomach puts an end to hunger-contractions.

Altogether fifteen rats, eight in one group and seven in the other, have

been tested and the results are definite and conclusive in spite of the small number of animals. The results are presented in table 1, which shows that there is a distinct difference in the number of stimulations necessary for conditioning under these two conditions. The groups overlap relatively little. Furthermore, it is noteworthy that the low score of Rat No. 13 occurred in an animal which appeared to be especially sensitive to the electric shock. We are therefore justified in concluding that the occurrence of hunger-contractions favors learning; and thus we fill in a lacuna in our information about the dependence of learning upon muscular tension in general.

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[2] A. J. Carlson, *The Control of Hunger in Health and Disease*, 1916; T. Wada, "An Experimental Study of Hunger in Its Relation to Activity," *Arch. Psychol.*, **8**, No. 57 (1922).

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[4] M. H. Powelson, "Gastric Transplantation," *Science*, **62**, 247–248 (1925).

[5] C. P. Richter, "A Behavioristic Study of the Activity of the Rat," *Comp. Psychol. Monog.*, **1**, No. 2 (1922).

[6] Powelson, loc. cit.

[7] Carlson, loc. cit.